JOC*Article*

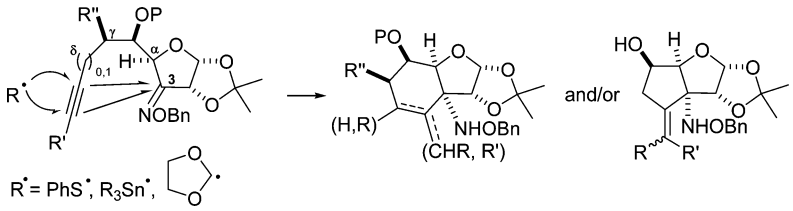
Formation of Five- and Six-Membered Carbocycles with Nitrogenated Tetrasubstituted Carbons by Radical Addition-Carbocyclization of Alkynyl Ketoxime Ethers

Marta Fernández-González and Ricardo Alonso*

Departamento de Química Orgánica y Unidad Asociada al CSIC, Universidad de Santiago de Compostela, 15782 Santiago de Compostela, Spain

qoraa@usc.es

Received April 27, 2006



C3-Ketoxime ethers bearing alkynes with terminal δ-yne or internal γ-yne functions were prepared in five or six steps and ~20% overall yield from commercial glucofuranose derivatives. Their thiyl-, stannyl-, or carbon radical-promoted addition−carbocyclization gave five- or six-membered carbocycles nitrogenated at one of the bridgehead positions. For internal γ-yne ethers the tandem process was strongly dependent on both the alkyne substituent and the radical-promoting species and could be directed toward either the five- or the six-membered carbocycle. These results are presented and discussed in the context of studies working toward (−)-tetrodotoxin.

Introduction

Free radical reactions are now well established in the synthetic repertoire.[1] In particular, the addition of carbon radicals to C=N bonds has become a reliable procedure for the synthesis of nitrogenated compounds.[2] However, the full potential of this reaction remains unrealized, especially its potential for the creation of nitrogen-bearing fully substituted carbon centers in complex polycyclic frameworks.[3] The study and development of this latter type of transformation is called for by the existence of a considerable number of useful or potentially useful compounds endowed with a carbon center of this kind.[4]

One example is the natural product tetrodotoxin (TTX, **10**, Scheme 1), a compound with significant chemical, biological, and pharmacological properties. Although it is a relatively small molecule (MW = 319), its structure is extremely complex. Besides its nitrogenated tetrasubstituted carbon at C8a, it features

* To whom correspondence should be addressed. Tel: +34 981547085. Fax: +34 981595012.

(1) (a) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions: Concepts, Guidelines, and Synthetic Applications*; VCH: Weinheim, Germany, 1996. (b) Giese, B.; Kopping, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. React.* **1996**, *48*, 301. (c) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177. (d) Renaud, P.; Gerster, M. *Angew. Chem., Int. Ed*. **1998**, *37*, 2562. (e) Sibi, M. P.; Porter, N. A. *Acc. Chem. Res.* **1999**, *32*, 163. (f) Naito, T. *Heterocycles* **1999**, *50*, 505. (g) *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: New York, 2001; Vols. 1 and 2. (h) Bar, G.; Parsons, A. F. *Chem. Soc. Rev.* **2003**, *32*, 251. (i) Sibi, M. P.; Manyam, S.; Zimmerman, J. *Chem. Rev.* **2003**, *103*, 3263.

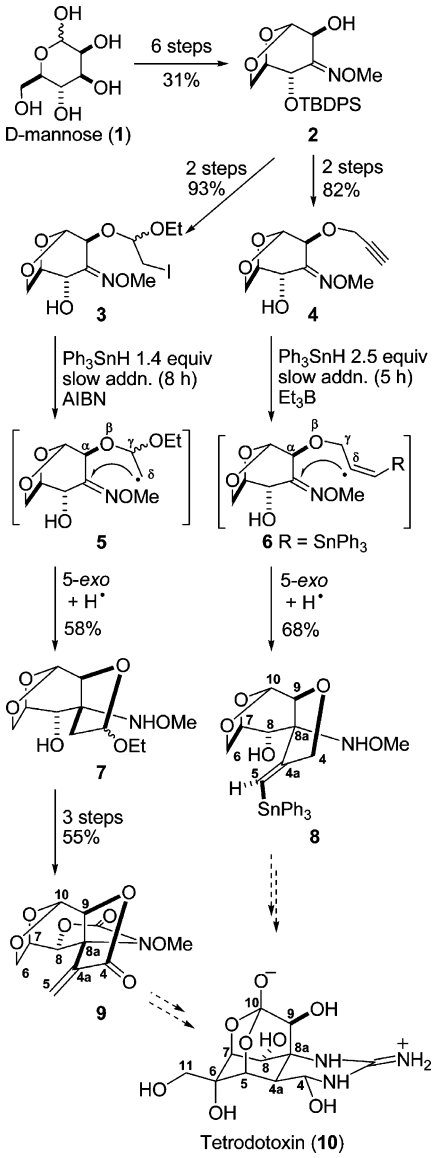
(2) For reviews on addition of radicals to C=N bonds, see: (a) Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543. (b) Martínez-Grau, A.; Marco-Contelles, *J. Chem. Soc. Rev.* **1998**, *27*, 155. (c) Friestad, G. K. *Tetrahedron* **2001**, *57*, 5461. (d) Novel Radical Traps, Kim, S.; Joon, J.-Y. In *Radicals in Organic Synthesis*, 1st ed.; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, New York, 2001; Vol. 2, Chapter 1. (e) Bertrand, M.; Feray, L.; Gastaldi, S. C. *R. Chimie* **2002**, *5*, 623. (f) Miyabe, H.; Ueda, M.; Naito, T. *Synlett* **2004**, 7, 1140.

(3) Although radical addition onto ketimines is receiving increased attention; see for example: (a) Miyabe, H.; Yamaoka, Y.; Takemoto, Y. *Synlett* **2004**, 2597. (b) Miyabe, H.; Yamaoka, Y.; Takemoto, Y. *J. Org. Chem.* **2005**, *70*, 3324. (c) Miyabe, H.; Yamaoka, Y.; Takemoto, Y. *J. Org. Chem.* **2006**, *71*, 2099 and references therein.

(4) Targets with fully substituted nitrogenated carbons include (−)-huperzine A [(a) Jiang, H.; Luo, X.; Bai, D. *Curr. Med. Chem.* **2003**, *10*, 2231], (−)-cephalotaxine [(b) Taniguchi, T.; Ishita, A.; Uchiyama, M.; Tamura, O.; Muraoka, O.; Tanabe, G.; Ishibashi, H. *J. Org. Chem.* **2005**, *70*, 1922], immunosuppressant FR901483 [(c) Panchaud, P.; Chabaud, L.; Landais, Y.; Ollivier, C.; Renaud, P.; Zigmantas, S. *Chem. Eur. J.* **2004**, *10*, 3606], (+)-halichlorine [(d) Clive, D. L. J.; Yu, M.; Wang, J.; Yeh, V. S. C.; Kang, S. *Chem. Rev.* **2005**, *105*, 4483], lactacystin [(e) Fukuda, N.; Sasaki, K.; Sastry, T. V. R. S.; Kanai, M.; Shibasaki, M. *J. Org. Chem.* **2006**, *71*, 1220], and myriocin [(j) Lee, K.-Y.; Oh, C.-Y.; Kim, Y.-H.; Joo, J.-E.; Ham, W.-H. *Tetrahedron Lett.* **2002**, *43*, 9361. (k) Brunner, M.; Koskinen, A. M. P. *Curr. Org. Chem.* **2004**, *8*, 1629].

10.1021/jo060883y CCC: $33.50
Published on Web 08/08/2006

SCHEME 1. 5-*exo* Radical-Based Route toward Tetrodotoxin via *O*-Tethered Alkyl and Vinyl Radicals[a]



[a] For details, see ref 18. Tetrodotoxin numbering is used.

a high heteroatom content (50% of non-H atoms), nine stereogenic centers (including all the carbons of its six-membered carbocycle), and the unique combination of an ortho-acid at C10 and a guanidine-hemiaminal ring.[5] Biological interest in tetrodotoxin stems from its exceptional potency and selectivity in blocking voltage-gated sodium channels.[6] By virtue of this property, tetrodotoxin has been instrumental in the identification, isolation, purification, and subsequent sequencing of the main subunit of these channels,[7] and it continues to be widely employed in biological studies.[8,9] Pharmacologically, tetrodotoxin is currently undergoing preclinical tests as a local and topical anaesthetic and also phase II studies of its utility for treatment of acute oncological or neuropathic pain and drug abuse withdrawal symptoms.[10,11]

Ever since the elucidation of its structure,[5] the unique, complex architecture of tetrodotoxin has made it a test bench for the development of synthetic methodologies.[12−16] In particular, the challenging tetrasubstituted nitrogenated stereocenter at C8a has been approached in different ways by a number of research groups.[17] Our own group, for example, has shown that this center can be formed with complete stereocontrol through 5-*exo* radical addition to the imino carbon of ketoxime ethers, as illustrated in Scheme 1 for the radical intermediates **5** and **6**.[18−20] This key transformation allows the conversion of β-D-mannopyranose (**1**) into compounds **8** and **9**, which have nine of the 11 carbon atoms of tetrodotoxin (all except the hydroxymethyl and guanidine carbons) and four of its stereocenters (C7, C8, C8a and C9) (Scheme 1).

The structural features of **8** and **9** and the relative short and effective 5-*exo* radical-based synthetic sequence leading to these structures (9 steps, 17% overall yield for **8**, 12 steps, 9% overall

(5) The structural determination of tetrodotoxin was reported at the 3rd IUPAC Symposium on the Chemistry of Natural Products, 13 April, 1964 (Kyoto, Japan), by the groups led by Hirata, Mosher, Tsuda and Woodward. (a) Goto, T.; Kishi, Y.; Takahashi, S.; Hirata, Y. *Tetrahedron* **1965**, *21*, 2059. (b) Mosher, H. S.; Fuhrman, F. A.; Buchwald, H. D.; Fischer, H. G. *Science* **1964**, *144*, 1100. (c) Tsuda, K.; Ikuma, S.; Kawamura, M.; Tachikawa, R.; Sakai, K.; Tamura, C.; Amakasu, O. *Chem. Pharm. Bull.* **1964**, *12*, 1357. (d) Woodward, R. B. *Pure Appl. Chem.* **1964**, *9*, 49.

(6) (a) *Tetrodotoxin, Saxitoxin, and the Molecular Biology of the Sodium Channel*; Kao, C. Y., Levinson, S. R., Eds.; New York Academy of Sciences: New York, 1986; Vol. 479. (b) Tikhonov, D. B.; Zhorov, B. S. *Biophys. J.* **2005**, *88*, 184. (c) Geffeney, S. L.; Fujimoto, E.; Brodie, E. D.; Brodie, E. D.; Ruben, P. C. *Nature* **2005**, *434*, 759.

(7) Noda, M.; Shimizu, S.; Tanabe, T.; Takai, T.; Ikeda, T.; Takahashi, H.; Hakayama, H.; Kanoaka, Y.; Minamino, N.; Kangawa, K.; Matsuo, H.; Raftery, M. A.; Hirose, T.; Inayama, S.; Hayashida, H.; Miyata, T.; Numa, S. *Nature* **1984**, *312*, 121.

(8) Hucho, F. *Angew. Chem.* **1995**, *107*, 23; *Angew. Chem., Int. Ed.* **1995**, *34*, 39.

(9) For the period 2000−2005, SciFinder Scholar retrieves between 270 and 400 references per year for tetrodotoxin in the CAS database. They mostly relate to neurological and pharmacological studies.

(10) Pharmacological studies of tetrodotoxin under various trade names are being conducted at Wex-Pharmaceuticals (Canada) and Esteve (Spain): http://www.wexpharma.com/products/tectin.htm; http://www.wexpharma.com/products/tocudin.htm; http://www.wexpharma.com/products/tetrodin.htm; http://www.esteve.es/EsteveFront/Proyectos.do?op=DP&div=id&con=14&cm=132.

(11) For recent papers on the therapeutic potential of sodium channel blockers, see: (a) French, R. J.; Terlau, H. *Curr. Med. Chem.* **2004**, *11*, 3053. (b) Wood, J. N.; Boorman, J. *Curr. Top. Med. Chem.* **2005**, *5*, 529.

(12) For the first total synthesis of racemic tetrodotoxin, see: (a) Kishi, Y.; Aratani, M.; Fukuyama, T.; Nakatsubo, F.; Goto, T.; Inoue, S.; Tanino, H.; Sugiura, S.; Kakoi, H. *J. Am. Chem. Soc.* **1972**, *94*, 9217. (b) Kishi, Y.; Fukuyama, T.; Aratani, M.; Nakatsubo, F.; Goto, T.; Inoue, S.; Tanino, H.; Sugiura, S.; Kakoi, H. *J. Am. Chem. Soc.* **1972**, *94*, 9219.

(13) Enantioselective total syntheses of tetrodotoxin have been achieved by the research groups led by Isobe and Du Bois: (a) Ohyabu, N.; Nishikawa, T.; Isobe, M. *J. Am. Chem. Soc.* **2003**, *125*, 8798. (b) Hinman, A.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 11510. (c) Nishikawa, T.; Urabe, D.; Isobe, M. *Angew. Chem.* **2004**, *116*, 4886; *Angew. Chem., Int. Ed.* **2004**, *43*, 4782.

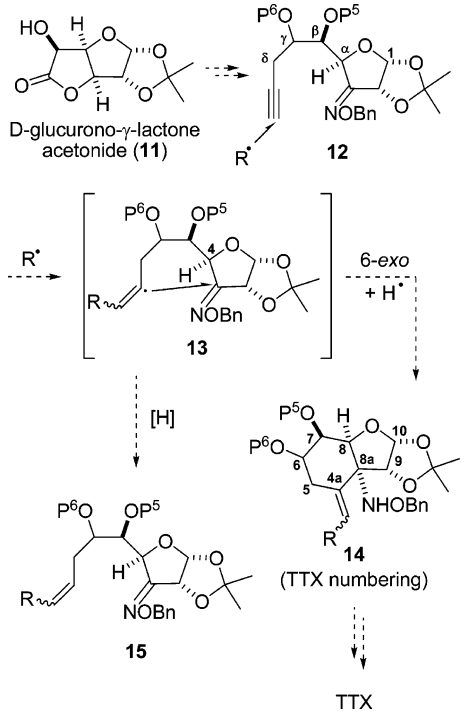
(14) The group led by Sato recently reported a new stereocontrolled synthesis of racemic tetrodotoxin: Sato, K.-i.; Akai, S.; Sugita, N.; Ohsawa, T.; Kogure, T.; Shoji, H.; Yoshimura, J. *J. Org. Chem.* **2005**, *70*, 7496.

(15) For syntheses of several deoxy-TTX forms, see: (a) Nishikawa, T.; Urabe, D.; Yoshida, K.; Iwabuchi, T.; Asai, M.; Isobe, M. *Pure Appl. Chem.* **2003**, *75*, 251. (b) Nishikawa, T.; Urabe, D.; Yoshida, K.; Iwabuchi, T.; Asai, M.; Isobe, M. *Chem. Eur. J.* **2004**, *10*, 452.

(16) For other synthetic efforts towards tetrodotoxin see the following articles and the references therein: (a) Keana, J. F. W.; Bland, J. S.; Boyle, P. J.; Erion, M.; Hartling, R.; Husman, J. R.; Roman, R. B.; Ferguson, G.; Parvez, M. *J. Org. Chem.* **1983**, *48*, 3627. (b) Nachman, R. J.; Honel, M.; Williams, T. M.; Halaska, R. C.; Mosher, H. S. *J. Org. Chem.* **1986**, *51*, 4802. (c) Burgey, C. S.; Vollerthun, R.; Fraser-Reid, B. *J. Org. Chem.* **1996**, *61*, 1609. (d) Itoh, T.; Watanabe, M.; Fukuyama, T. *Synlett* **2002**, 1323. (e) Ohtani, Y.; Shinada, T.; Ohfune, Y. *Synlett* **2003**, 619. (f) Taber, D. F.; Storck, P. H. *J. Org. Chem.* **2003**, *68*, 7768. (g) Ozores, L.; Cagide, F.; Alonso, R. *Synlett* **2004**, 2746.

(17) Synthetic methods applied to the construction of the C8a stereocenter of tetrodotoxin include Beckman rearrangement (ref 12), Rh-carbene C−H insertion (ref 13b), Overman rearrangement (ref 13c), and azide opening of spiro α-chloroepoxides (ref 14).

SCHEME 2. Tandem Addition−6-*exo* Carbocyclization Radical-Based Route toward Tetrodotoxin via a Ketoxime Ether Bearing a Terminal Alkyne[a]

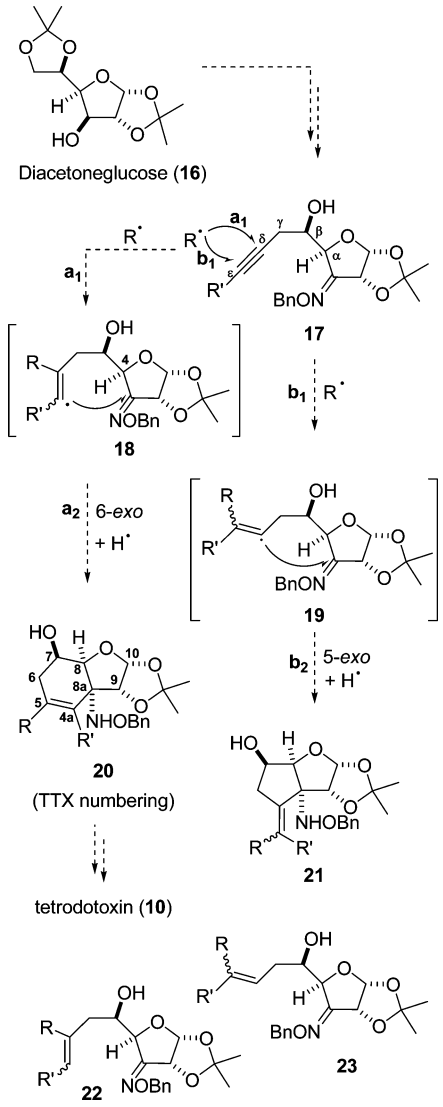


[a] Sugar numbering is used except for **14**.

yield for **9**) suggest that both might serve as intermediates in the total synthesis of tetrodotoxin. However, in this paper we describe significant shorter routes to the alternative intermediates **14** (Scheme 2) and **20** (Scheme 3), both of which were prepared by strategies featuring as their key step a tandem radical addition−6-*exo*-carbocyclization undergone by a ketoxime ether bearing an alkyne in which the triple bond was terminal in **12** (Scheme 2) and internal in **17** (Scheme 3, path **a**). Both **14** and **20** feature both the nitrogenated tetrasubstituted C8a stereocenter of tetrodotoxin and its six-membered carbocycle with most of its functionality, and they appear capable of mediating shorter routes to the toxin than **8** or **9**.[21]

As well as by its relevance to the synthesis of tetrodotoxin, this work was strongly motivated by the novelty and potential scope of the tandem radical processes **12** → **14** and **17** → **20** (+ **21**), no examples of which have hitherto been reported.[22−27] We envisage that the methodology described herein will find increasing use for the formation of carbocyles with nitrogenated quaternary carbons.[28]

SCHEME 3. Tandem Addition−6-*exo* Carbocyclization Radical-Based Route toward Tetrodotoxin via a Ketoxime Ether Bearing an Internal Alkyne (Pathway a); Alternative 5-*exo* Carbocyclization Leads to *cis*-Fused Cyclopentafurans (Pathway b)[a]



[a] Sugar numbering is used except for **20**.

Results and Discussion

Synthesis of Alkynyl Ketoxime Ethers 12a and 17a−c. The δ-alkynyl ketoxime ether **12a** [6*R*-**12**, $P^5 + P^6 = C(CH_3)_2$, Scheme 4] was obtained from commercial D-glucurono-γ-lactone acetonide (**11**).[29] Treatment of **11** with 1-trimethylsilylpropynyllithium[30] afforded **24** in 88% yield as a mixture of C6-epimeric hemiketals.[31] Hydride reduction of the masked carbonyl group in **24**, carried out by treatment with $NaBH_3CN$

(18) (a) Noya, B.; Alonso, R. *Tetrahedron* Lett. **1997**, *38*, 2745. (b) Noya, B.; Paredes, M. D.; Ozores, L.; Alonso, R. *J. Org. Chem.* **2000**, *65*, 5960.

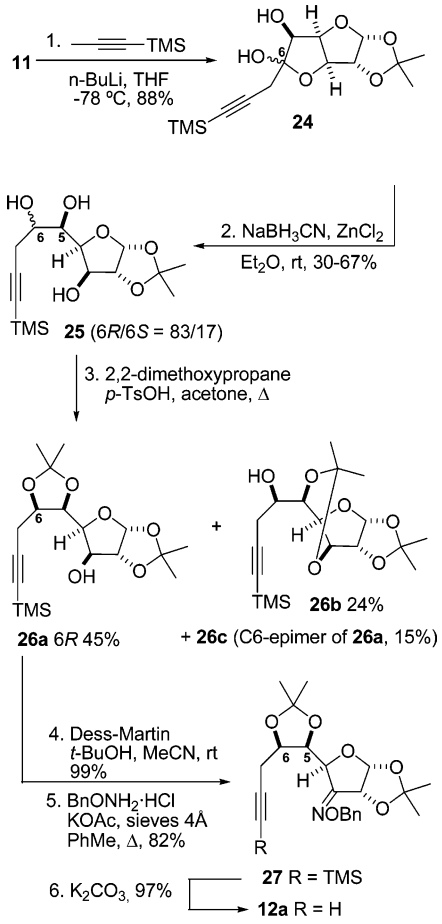
(19) Nitrogenated tetrasubstituted carbons can also be formed by intermolecular radical addition of α-oxygenated carbon radicals to α-alkoxycarbonyl ketoxime ethers: Torrente, S.; Alonso, R. *Org. Lett.* **2001**, *3*, 1985.

(20) The intra- and intermolecular 1,3-dipolar cycloaddition of ketonitrones has also proved to be a convenient method for stereoselective formation of nitrogenated tetrasubstituted centres: (a) Torrente, S.; Noya, B.; Paredes, M. D.; Alonso, R. *J. Org. Chem.* **1997**, *62*, 6710. (b) Torrente, S.; Noya, B.; Branchadell, V.; Alonso, R. *J. Org. Chem.* **2003**, *48*, 4772.

(21) Although the total synthesis of a molecule as complex as tetrodotoxin is a noteworthy achievement even if it involves a large number of steps, particular emphasis is now placed on practicability and hence on brevity: Koert, U. *Angew. Chem.* **2004**, *116*, 5690; *Angew. Chem., Int. Ed.* **2004**, *43*, 5572.

(22) There have been no reports of the formation of cyclohexane derivatives with a fully substituted nitrogenated carbon by *tandem* radical addition−6-*exo carbo*cyclizations of ketimine derivatives with either a terminal δ-yne or an internal γ-yne. Certain ketoxime ethers with a terminal δ-yne derived from cyclobutanone have been reported to undergo a cascade consisting in radical addition, 6-*exo* carbocyclization, fragmentation, transannulation, ring expansion, and elimination, the ketoxime ether group remaining unaltered or being hydrolyzed to a keto group overall. See: (a) Pattenden, G.; Schulz, D. *Tetrahedron Lett.* **1993**, *34*, 6787. (b) Hollingworth, G. J.; Pattenden, G.; Schulz, D. J. *Aust. J. Chem.* **1995**, *48*, 381.

SCHEME 4. Synthesis of δ-Alkynyl Ketoxime Ether 12a[a]



[a] Sugar numbering is used.

and $ZnCl_2$, gave the corresponding triols **25** with an average yield of 49% and reasonable stereoselectivity (6*R*/6*S* = 83/17).[32,33] Selective protection with 2,2-dimethoxypropane and *p*-TsOH in acetone allowed the separation of the (6*S*)-C5,C6 isopropylidene derivative **26a** (45%) from its (6*S*)-C3,C5 acetonide isomer **26b** (24%) and its C6-epimer **26c** (15%).[34−36] A similar reaction path through the 5-*O*-methoxymethyl derivative of **11** gave **26a** in 21% overall yield.[37] Dess−Martin oxidation[38] of **26a** at its free hydroxyl group, formation of the benzyl oxime ether **27**, and final TMS deprotection all proceeded uneventfully in good yields, affording the desired ketoxime ether **12a** (6 steps, 10−20% overall from **11**).

The cyclization precursors **17a**−**c** were prepared from diacetoneglucose (**16**) through the five-step sequence indicated in Scheme 5. Oxidation[39] and oxime ether formation[40] at C3, followed by hydrolysis of the terminal acetonide (best accomplished with Dowex 50W-X8),[41] afforded the C5,C6 deprotected C3-ketoxime ether **28**, which was then transformed into epoxide 5*S*-**29** under Mitsunobu-type conditions. [The configuration of 5*S*-**29** at C5, which agrees with published prece-

(23) G. Fu and co-workers reported one example of simultaneous formation of a nitrogenated quaternary centre and a cyclohexane ring by tandem radical addition−6-*exo* carbocyclization of a ketoxime ether carrying a ϵ-formyl group (44%): (a) Tormo, J.; Hays, D. S.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 201. For a related 6-*endo* case, see: (b) Tomaszewski, M. J.; Warkentin, J. *Tetrahedron Lett.* **1992**, *33*, 2123.

(24) There have been two reported cases of the simultaneous formation of a nitrogenated quaternary centre and a cyclohexane ring by 6-*exo carbo*cyclizations of a primary alkyl radical generated from either a C−Br or a C−Se bonds to a ketimine group: (a) Della, E. D.; Knill, A. M. *Aust. J. Chem.* **1994**, *47*, 1833. (b) Bowman, W. R.; Stephenson, P. T.; Young, A. R. *Tetrahedron Lett.* **1995**, *36*, 5623.

(25) For the tandem radical addition−6-*exo hetero*cyclization of benzyl ketoxime ethers with an *N*-tethered terminal δ-yne to give benzo-fused piperidines, see: (a) Enholm, E. J.; Burroff, J. A.; Jaramillo, L. M. *Tetrahedron Lett.* **1990**, *31*, 3727. For analogous nontandem cyclizations with *O*-tethered alkynes, see: (b) Booth, S. E.; Jenkins, P. R.; Swain, C. J. *J. Chem. Soc., Chem. Commun.* **1991**, 1248. (c) Booth, S. E.; Jenkins, P. R.; Swain, C. J.; Sweeney, J. B. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3499.

(26) Tandem radical addition-cyclization processes not involving ketimine derivatives have been reported by a number of groups. Selected examples: the addition−5-*exo* carbocyclization of alkyne-tethered aldoxime ethers derived from carbohydrates [(a) Marco-Contelles, J.; Destabel, C.; Gallego, P.; Chiara, J. L.; Bernabé, M. *J. Org. Chem.* **1996**, *61*, 1354]; the addition-cyclization of allene-tethered aldoxime ethers and hydrazones [(b) Marco-Contelles, J.; Balme, G.; Bouyssi, D.; Destabel, C.; Henriet-Bernard, C. D.; Grimaldi, J.; Hatem, J. M. *J. Org. Chem.* **1997**, *62*, 1202]; the PhS•-promoted addition-6-*exo*-carbocyclization of aldoxime ethers with a γ-C≡C−Ar group [(c) Keck, G. E.; Wager, T. T.; Rodriquez, J. F. D. *J. Am. Chem. Soc.* **1999**, *121*, 5176]; the tandem cyclization of 2-azetidinone-tethered enynes and allenynes [(d) Alcaide, B.; Rodríguez-Campos, I. M.; Rodríguez-López, J.; Rodríguez-Vicente, A. *J. Org. Chem.* **1999**, *64*, 5377. (e) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Org. Lett.* **2003**, *5*, 3795]; a number of addition-heterocyclization processes of *O*- or *N*-tethered unsaturated carbon chains [(f) Hanessian, S.; Ninkovic, S. *J. Org. Chem.* **1996**, *61*, 5418. (g) Gagosz, F.; Zard, S. Z. *Org. Lett.* **2002**, *4*, 4345. (h) Pedrosa, R.; Andrés, C.; Duque-Soladana, J. P.; Maestro, A.; Nieto, J. *Tetrahedron: Asymmetry* **2003**, *14*, 2985. (i) Friestad, G. K.; Jiang, T.; Fioroni, G. M. *Tetrahedron Asymmetry* **2003**, *14*, 2853. (j) Friestad, G. K.; Massari, S. E. *J. Org. Chem.* **2004**, *69*, 863. (k) Sibi, M. P.; Patil, K.; Rheault, T. R. *Eur. J. Org. Chem.* **2004**, 372. (l) Miyabe, H.; Ueda, M.; Fujii, K.; Nishimura, A.; Naito, T. *J. Org. Chem.* **2003**, *68*, 5618. (m) Miyabe, H.; Naito, T. *Org. Biom. Chem.* **2004**, *2*, 1267. (n) Miyata, O.; Kajisa, S.; Ueda, M.; Yamauchi, M.; Naito, T. *Chem. Pharm. Bull.* **2005**, *53*, 995]; the addition-cyclization of aromatic tertiary amines and furanones [(o) Marinkovic, S.; Hoffmann, N. *Eur. J. Org. Chem.* **2004**, 3102]; a thiophenol-mediated addition-translocation-cyclization process [(p) Beaufils, F.; Denes, F.; Renaud, P. *Org. Lett.* **2004**, *6*, 2563]; the addition-cyclization of 2-indolylacyl radicals with electron-deficient alkenes [(q) Bennasar, M.-Ll.; Roca, T.; Griera, R.; Bosch, J. *J. Org. Chem.* **2001**, *66*, 7547].

(27) For reviews on radical addition−cyclization processes and their synthetic application, see: (a) Naito, T. *Heterocycles* **1999**, *50*, 505. (b) Okiko, M.; Naito, T. *C. R. Acad. Sci., Ser. IIc: Chim.* **2001**, *4*, 401.

(28) We recently published a preliminary account of the thiyl-mediated tandem radical addition and cyclization of ϵ-substituted γ-yne-ketimines: Fernández, M.; Alonso, R. *Org. Lett.* **2005**, *7*, 11.

(29) D-Glucurono-γ-lactone acetonide (**11**) is commercially available. It can also easily be prepared from cheaper unprotected D-glucurono-γ-lactone: (a) Kithihara, T.; Ogawa, T.; Naganuma, T.; Matsui, M. *Agric. Biol. Chem.* **1974**, *38*, 2189. (b) Yoda, H.; Nakaseko, Y.; Takabe, K. *Synlett* **2002**, 1532.

(30) (a) Corey, E. J.; Kirst, H. A. *Tetrahedron Lett.* **1968**, *9*, 5041. (b) Stork, G.; Kowalski, C.; Garcia, G. *J. Am. Chem. Soc.* **1975**, *97*, 3258.

(31) For the reaction of the 5-*O*-*tert*-butyldimethylsilyl derivative of **11** with various anions to form the corresponding hemiketal intermediates as C6-epimeric mixtures, see: (a) Graβberger, V.; Berger, A.; Dax, K.; Fechter, M.; Gradnig, G.; Stütz, A. E. *Liebigs Ann. Chem.* **1993**, 379. (b) Blériot, Y.; Veighey, C. R.; Smelt, K. H.; Cadefau, J.; Stalmans, W.; Biggadike, K.; Lane, A. L.; Müller, M.; Watkin, D. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **1996**, *7*, 2761. (c) Blériot, Y.; Masaguer, C. F.; Charlwood, J.; Winchester, B. G.; Lane, A. L.; Crook, S.; Watkin, D. J.; Fleet, G. W. J. *Tetrahedron* **1997**, *53*, 15135. (d) Masaguer, C. F.; Blériot, Y.; Charlwood, J.; Winchester, B. G.; Fleet, G. W. J. *Tetrahedron* **1997**, *53*, 15147. (e) Morin, C.; Ogier, L. *Tetrahedron: Asymmetry* **2000**, *11*, 629. (f) Bessieres, B.; Morin, C. *Synlett* **2000**, 1691.

(32) Kim, S.; Oh, C. H.; Ko, J. S.; Ahn, K. H.; Kim, Y. J. *J. Org. Chem.* **1985**, *50*, 1927.

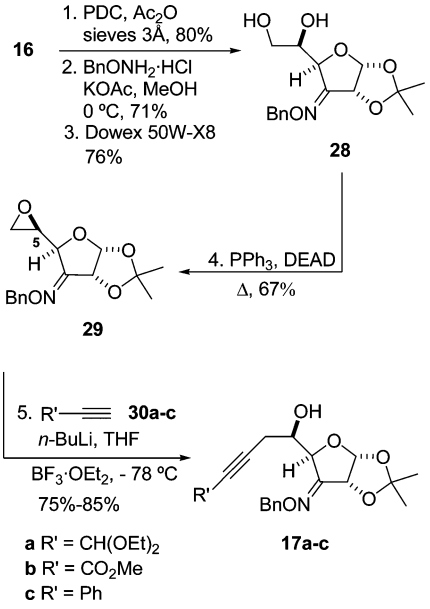
(33) Other reduction conditions ($NaBH_4$/MeOH, $LiAlH_4$/Et_2O or $NaBH_4$/$CeCl_3$/MeOH) gave lower yields.

(34) For details of the structural characterization of the synthetic intermediates and the cyclized products resulting from the tandem radical processes, see Experimental Section and Supporting Information.

(35) The relative stereochemistry of **26a** at C6 was deduced from ^1H NMR coupling constants and NOE data obtained for its cyclized derivatives **14** (Scheme 2 and Table 1). See Supporting Information.

(36) Treatment of the mixture of **26b** and **26c** with 2,2-dimethoxypropane and *p*-TsOH in acetone allowed partial conversion of **26b** into **26a**, which was then separated from the remaining **26b** and unaltered **26c** by chromatography.

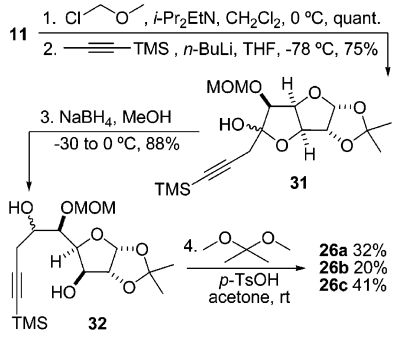
SCHEME 5. Synthesis of γ-Alkynyl Ketoxime Ethers 17



dents,[42] was eventually confirmed by spectroscopic studies of its cyclic derivatives **20** (Table 2) and by an X-ray study of **20cs** (vide infra)]. Epoxide opening at C6 by the lithium anions derived from the terminal alkynes **30a**−**c** in the presence of $BF_3{\cdot}OEt_2$[43] finally afforded the desired γ-alkynyl ketoxime ethers **17a**−**c** in 21−24% overall yields from **16**.[44]

Tandem Radical Addition−**Cyclizations.** The tandem radical addition-cyclization of terminal alkyne **12a** was first attempted under conditions similar to those employed for the successful 5-*exo* cyclization of the *O*-tethered γ-alkynylketoxime ether **4** (Scheme 1), i.e., using tin radicals as promoters ($R^{\bullet}$ in Schemes 2 and 3). Alkynes **12** were expected to behave similarly to **4** in the first step of the tandem process, undergoing intermolecular addition of tin radicals to form vinyl radical intermediates **13** (Scheme 2) in much the same way as **4** gives **6** (Scheme 1). However, the second step appeared less likely for **13** than for **6**, because the 6-*exo* cyclization required for **13** is expected to be slower than the 5-*exo* process of **6**.[45] Moreover, **13** (but not **6**) could undergo competitive reduction through 1,5-H transfer from position 4 (**13** → **15**, Scheme 2).[46] In the event, slow addition of *n*-Bu_3SnH (2 equiv) to a 0.02 M solution of **12a** in toluene over 2.5 h resulted in no reaction, **12a** being essentially recovered unaltered (Table 1, entry 1). By contrast, the whole desired tandem process took place when promoted by photochemically generated thiyl radicals. Irradiation of a 0.02 M solution of **12a** and PhSH (1 equiv) in toluene with a 450-W medium-pressure mercury lamp led to cyclohexane derivative **14as**, which was isolated in 33% yield as a 6:4 mixture of geometric isomers (Table 1, entry 2).[47] Among other minor products, this reaction also produced what was tentatively identified as a geometric mixture of noncyclic PhSH-addition products (**15as**, 15%).[48] The yield of **14as** improved to 55%, without affecting that of **15as**, when the reaction was conducted in benzene at greater dilution (0.014 M) and with a greater load of PhSH, 1.3 equiv (Table 1, entry 3). Finally, we found that tin radicals also promoted the tandem process if the stannane precursor (2−2.4 equiv) was added in one portion at the beginning of the reaction (Table 1, entries 4 and 5) instead of slowly over a long period. Under these conditions, **12a** afforded the desired product in yields that were better than with PhSH (60−61% as against 33−55%) and just slighter lower than the yield of **8** obtained from **4** (68%, Scheme 1). Importantly, the *n*-Bu_3Sn-derived cyclohexyl derivative **14at** was mainly obtained as its *E* isomer (*E*/*Z* ratio 92:8) and the mixture was easily separated. This is an advantage if subsequent vinyl couplings are planned.[49]

(37) The alternative preparation of **26a** from **11** was performed as shown below; for details, see the Supporting Information.



(38) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Tojo, G.; Fernández, M. In *Basic Reactions in Organic Synthesis, Oxidation of Alcohols to Aldehydes and Ketones*; Tojo, G., Ed.; Springer: New York, 2006; Chapter 3.

(39) Oxidation of diacetoneglucose has been carried out a number of times. For selected examples, see: (a) Beynon, P. J.; Collins, P. M.; Doganges, P. T.; Overend, W. G. *J. Chem. Soc. C* **1966**, 1131. (b) Czennecki, B.; Ceorcoulis, C.; Stevens, C. L.; Vijayakumapae, K. *Tetrahedron Lett.* **1985**, *26*, 1699. (c) Hodosi, G. *Carbohydr. Res.* **1994**, *252*, 291.

(40) (a) Plenkiewicz, J.; Szarek, W. A.; Sipos, P. A.; Phibbs, M. K. *Synthesis* **1974**, 56. (b) Denmark, S. E.; Dappen, M. S. *J. Org. Chem.* **1984**, *49*, 798.

(41) (a) Park, K. H.; Yoon, Y. J.; Lee, S. G. *Tetrahedron Lett.* **1994**, *35*, 9737. Hydrolysis of the terminal acetonide with 30% aqueous AcOH [(b) Verheyden, J. P. H.; Richardson, A. C.; Bhatt, R. S.; Grant, B. D.; Fitch, W. L.; Moffatt, J. G. *Pure Appl. Chem.* **1978**, *50*, 1363] and with thiourea [(c) Majumdar, S.; Bhattacharjya, A. *J. Org. Chem.* **1999**, *64*, 5682] gave lower yields (34% and 24%, respectively).

(42) For the conversion of terminal diols into epoxides with retention under Mitsunobu conditions, see for example: (a) Achab, S.; Das, B. C. *Synth. Commun.* **1982**, *12*, 931. (b) Takano, S.; Seya, K.; Goto, E.; Hirama, M.; Ogasawara, K. *Synthesis* **1983**, 116. (c) Robinson, P. L.; Barry, C. N.; Bass, S. W.; Jarvis, S. E.; Evans, S. A. *J. Org. Chem.* **1983**, *48*, 5396. (d) Abushanab, E.; Bessodes, M.; Antonakis, K. *Tetrahedron Lett.* **1984**, *25*, 3841. (e) Mikkilineni, A. B.; Kumar, P.; Abushanab, E. *J. Org. Chem.* **1988**, *53*, 6005.

(43) (a) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391. (b) Le Merrer, Y.; Gravier-Pelletier, C.; Micas-Languin, D.; Mestre, F.; Duréault, A.; Depezay, J.-C. *J. Org. Chem.* **1989**, *54*, 2409. (c) Ramana, C. V.; Srinivas, B.; Puranik, V. G.; Gurjar, M. K. *J. Org. Chem.* **2005**, *70*, 8216.

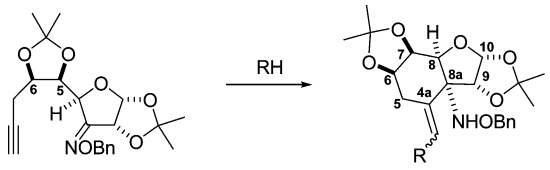
(44) Ketoxime ethers **17a**−**c** were obtained as a mixture of geometric isomers. For details see Supporting Information.

(45) In general, 6-*exo* cyclizations (as required for intermediates **13** in their conversion to **14**, Scheme 2) are slower than 5-*exo* cyclizations (as undergone by **6** to give **8**, Scheme 1). Moreover, the presence of O and N atoms in the chain connecting the carbon radical and the radical trap is known to accelerate 5-*exo* radical cyclizations for stereoelectronic reasons. The 6-*exo* process **13** → **14** is, on the contrary, a presumably slower *carbo*cyclization.

(46) ,5-Hydrogen transfers are especially favoured for stereoelectronic reasons. Moreover, for the particular case of radical **13**, the transfer of H4 is further facilitated by the presence of the ring oxygen (Scheme 2). This factor was particularly worrying because even for intermediate **6**, which cannot be reduced by a 1,5-H transfer but only intermolecularly, reduction partially competed with its 5-*exo* cyclization. See ref 18 for details.

(47) The major geometric isomer of **14at** was shown to be the *E*-isomer, in which the R group is oriented away from the crowded C8a quaternary centre, according to NOE data (see Supporting Information); the major geometric isomers of compounds **14as**, **21bs**, **21bt$_1$**, and **21bt$_2$** were assumed to have the same *E*-configuration.

TABLE 1. Tandem Addition−6-*exo* Carbocyclizations of *δ*-Alkynyl Ketoxime Ether 12a Promoted by Tin and Thiyl Radicals[a]

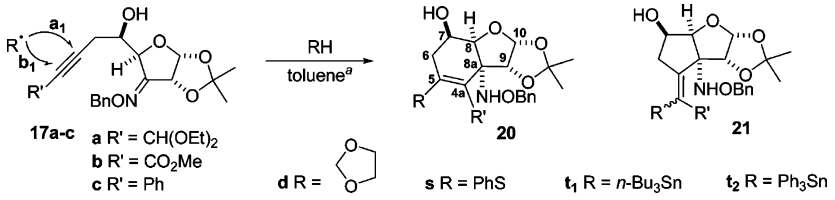


12a **14as** R = PhS **14at** R = *n*-Bu_3Sn

entry	RH, equiv	initiation, equiv	[**12a**][b]	time[c]	product yield[d] (*E*/*Z*)
1	*n*-Bu_3SnH, 2,[e]	AIBN, 1.9, Δ	0.02	2.5	*f*
2	PhSH, 1	450-W Hg[g]	0.02	2.5	**14as** 33, (60/40) **15as** 15[h]
3[i]	PhSH, 1.3	450-W Hg[g]	0.014	5.5	**14as** 55, (56/44) **15as** 15[h]
4	*n*-Bu_3SnH, 2.4	Et_3B, 1.37, Δ	0.02	6.25	**14at** 60, (92/8)
5	*n*-Bu_3SnH, 2	AIBN, 1, Δ	0.02	2	**14at** 61[j]

[a] Unless otherwise indicated, reactions were carried out in toluene that had been deoxygenated by bubbling Ar for 15 min. [b] Molar concentration of **12a**. [c] Reaction time in h. [d] Isolated yield. [e] Added over 2.5 h. [f] Starting **12a** was recovered. [g] A 450-W medium-pressure Hg UV lamp and Pyrex reaction vessels were employed; temperature was maintained below 40 °C. [h] For the tentative identification of **15as** as a mixture of geometric isomers of noncyclic PhSH-addition products, see ref 48. [i] Solvent was benzene. [j] *E*-**14at** was isolated in 61% yield; the *Z* isomer was not quantified.

TABLE 2. Tandem Addition−5-*exo* Carbocyclizations and/or Tandem Addition−6-*exo* Carbocyclizations of *δ*-alkynyl Ketoxime Ethers 17a−c Promoted by Tin, Thiyl, and 1,3-Dioxolan-2-yl Radicals



17a-c **a** R′ = $CH(OEt)_2$ **b** R′ = CO_2Me **c** R′ = Ph **d** R = **20** **21** **s** R = PhS **t₁** R = *n*-Bu_3Sn **t₂** R = Ph_3Sn

entry	substrate	RH, equiv	initiation, equiv, additives	[M]	time[b]	product yield[c]
1	**17a,b**	Ph_3SnH, 1.5[d]	AIBN, 2, Δ	0.015	14	*e*
2	**17a,b**	Ph_3SnH, 2.6[d]	Et_3B, 1, Δ	0.015	14	*e*
3	**17a**	PhSH, 1.2[d]	AIBN, 0.1, Δ	0.06	6	*e*
4	**17a**	PhSH, 3	sunlamp[f]	0.02	6.5	*g*
5	**17b**	PhSH, 1.3[d]	AIBN, 0.2, Δ	0.08	9.5	**20bs** 14, **21bs** 41,[h] **17b** 21
6	**17b**	PhSH, 0.6 + 0.6[i]	AIBN, 0.6, sunlamp[f]	0.08	19	**20bs** 11, **21bs** 29,[h] **17b** 58
7	**17b**	PhSH, 1.1 + 0.4[j]	hν,[k] benzene	0.04	6	**20bs** 24, **21bs** 20[h]
8	**17b**	1,3-dioxolane[l]	Ph_2CO, 1, hν[k]	0.04	2.25	**20bd** 65
9	**17c**	PhSH, 1.3[d]	AIBN, 0.1, Δ	0.08	9	**20cs** 50
10	**17c**	PhSH, 1.28,[m]	AIBN, 0.45, sunlamp[f]	0.075	7.5	**20cs** 45−54
11	**17c**	PhSH, 2.1	AIBN, 0.45, ultrasound[n]	0.036	9.5	**20cs** 61
12	**17c**	PhSH, 1.05	hν,[k] benzene	0.02	3	**20cs** 75, 7*E*+*Z*-**22cs** 6+6°
13	**17b**	PhSSPh, 0.7	hν,[k] benzene	0.027	5	**20bs** 22, **21bs** 5.7,[h] **17b** 10
14	**17c**	PhSH, 1.44,[m]	AIBN, 0.45,[f] $Yb(OTf)_3$, 0.2	0.08	11.5	**20cs** 42
15	**17c**	PhSH, 1.5,[m]	AIBN, 0.5,[f] $MgBr_2.OEt_2$, 0.6	0.08	19	**20cs** 40
16	**17b**	*n*-Bu_3SnH, 2	AIBN, 1, Δ	0.02	1.25	**20bt₁** 26, *E*-**21bt₁** 53[p]
17	**17b**	Ph_3SnH, 2	AIBN, 1, Δ	0.02	4.5	**20bt₂** 9, *E*-**21bt₂** 75[p]
18	**17c**	*n*-Bu_3SnH, 2	AIBN, 1, Δ	0.02	1.75	**20ct₁** 91

[a] Unless otherwise stated, the solvent was deoxygenated toluene. [b] Reaction time in h. [c] Isolated yield. [d] Added over 2.5 h (entry 2) or 3.5 h (entries 1, 3, 5, and 9). [e] Starting **17** was recovered. [f] A 300-W sunlamp was used as the radiation source. [g] Complex mixture. [h] Isolated as *E*/*Z* mixtures; see ref 47. [i] After 16 h. [j] After 4 h. [k] A 450-W medium-pressure Hg UV lamp and Pyrex reaction vessels were employed; temperature was maintained below 40 °C. [l] 1,3-Dioxolane also acted as the solvent. [m] PhSH was added in 2−3 portions. [n] The flask was immersed in the bath of an ultrasound cleaning device. [o] See ref 50. [p] See ref 47.

Initial uncertainty as to whether the γ-alkynyl ketoxime ethers **17** could be converted into cyclohexene derivatives **20** as in Scheme 3 (steps $\mathbf{a_1}$ and $\mathbf{a_2}$) arose first from the unknown influence of the terminal substituent R′, second from the possibility of a competitive tandem process leading to the exomethylenecyclopentane derivatives **21** (Scheme 3, steps $\mathbf{b_1}$ and $\mathbf{b_2}$), and third from the possibility of reduction of **17** to **22** or **23**. In fact, as earlier reported,[28] neither **17a** (R′ = $CH(OEt)_2$) nor **17b** (R′ = CO_2Et) reacted with thermally generated $Ph_3Sn^•$ (1.5−2.6 equiv, slow addition, Table 2, entries 1 and 2), nor was the cyclization of **17a** promoted by $PhS^•$ radicals, which either failed to react or gave a complex mixture (Table 2, entries 3 and 4). Gratifyingly, however, our preliminary study[28] showed that **17** could be cyclized to predominantly give either the exomethylenecyclopentane derivatives **21** (R′ = CO_2Et and R$^•$ = $PhS^•$, Table 2, entries 5−7) or the cyclohexene derivatives **20** (R′ = CO_2Et and R$^•$ = 1,3-dioxolanyl, entry 8; R′ = Ph and R$^•$ = $PhS^•$, entries 9−12)[50] under a variety of reaction conditions.

Now, we have performed additional experiments with the goal of increasing the efficiency of the radical addition−carbocyclization process. In particular, we explored the use of PhSSPh

instead of PhSH as the source of phenylthiyl radicals (entry 13) and the addition of Lewis acids[51] ($Yb(OTf)_3$, $MgBr_2{\cdot}OEt_2$, 0.2−0.6 equiv, entries 14 and 15) with no improvement. We next found that, as with **12a**, in the cases of of **17b** and **17c**, stannane did promote the tandem process when added in one portion at the beginning of the reaction, instead of over several hours. Furthermore, the overall yields it achieved were very good, 79−84% for **17b** (entries 16 and 17) and 91% for **17c** (entry 18), though in the case of **17b** the major product was the cyclopentyl derivative **21bt** [**21bt**:**20bt** ratio 53%:26% (entry 16) or 75%:9% (entry 17)]. Interestingly, both $\mathbf{21bt_1}$ (R = *n*-Bu_3Sn) and $\mathbf{21bt_2}$ (R = Ph_3Sn) were isolated as a single geometric isomer, whereas **21bs** (R = PhS) had been isolated as a nearly equimolar mixture of two geometric isomers.[47] The 91% of $\mathbf{20ct_1}$ obtained from **17c** with *n*-$Bu_3Sn^{\bullet}$ was the only cyclized product (entry 18).

Conclusions

The above results show that ketoxime ethers bearing terminal δ-yne or internal γ-yne functions can undergo tandem radical addition−carbocyclization. These processes accomplish in a single step both the formation of a carbocycle and the generation of a fully substituted nitrogen-bearing carbon atom. With terminal δ-ynes the product is an exomethylene cyclohexane; with internal γ-ynes the formation of either an exomethylene cyclopentane or a cyclohexene is possible. Tin radicals are more efficient promoters than thiyl radicals in every case examined and are also more selective when forming exomethylenes, giving mainly or exclusively just one of the geometric isomers.

The attractive characteristics of this methodology include the ease with which the ketoxime ether precursors can be prepared; the robustness of the triple bond and ketoxime ether functionalities; the smooth tandem reaction conditions, of critical importance when dealing with highly functionalized compounds; the possibility, when using γ-alkynylketoxime ethers, of directing the course of the process to obtain structurally diverse products from a common precursor; the structural or functional features of the final products (nitrogenated quaternary carbon, vinyl tin or sulfide, allylamine, predictably located internal or exocyclic double bonds, etc.), which can be of interest both in themselves and with regard to further synthetic transformations; and the possibility of further extending the scope of the methodology by varying the C═N radical acceptor, the chain connecting the alkyne and the C═N, and/or the reaction-initiating free radical $R^{\bullet}$.

As regards the synthesis of tetrodotoxin, although compounds such as **14** or **20** could probably be transformed into tetrodotoxin analogues or perhaps into the toxin itself, the methodology presented in this paper will probably be most efficiently exploited if applied to ketoxime ethers bearing alkynes that already contain more of the tetrodotoxin structure than is present in **12** or **17**. Research along these lines is being carried out and progress will be reported in due course.

Experimental Section

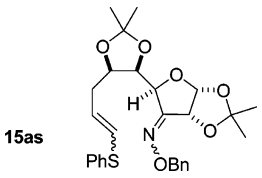
Procedures for Tandem Radical Addition−Carbocyclizations. Tin Radicals (Procedure A). A solution of **12a**, **17b**, or **17c** and AIBN (100 mol %) in dry toluene (0.02 M) was deoxygenated by bubbling argon for 15 min. R_3SnH (200 mol %) was added, and the mixture was refluxed until the starting material was consumed (TLC). Solvent removal, followed by flash chromatography using EtOAc/hexane mixtures, afforded the corresponding carbocyclic amine derivative.

Phenylthiyl Radicals (Procedure B). A solution of **12a**, **17b**, or **17c** in dry benzene (0.014−0.04 M) was deoxygenated by bubbling argon for 10−15 min. Thiophenol (100−150 mol %) was added either in one portion or in several portions at intervals through the reaction, and the mixture, maintained at <40 °C, was externally irradiated with a 450-W medium-pressure Hg UV lamp until the starting material was consumed (TLC). Solvent removal, followed by flash chromatography using EtOAc/hexane mixtures, afforded the corresponding carbocyclic amine derivative.

Cyclohexanamine 14as. Prepared by procedure B from **12a** (95 mg, 0.23 mmol) and thiophenol (0.31 mmol; 14 μL, followed by two additional 9 μL portions 1.5 and 2.5 h later) in dry benzene (17 mL). Irradiation time: 5.5 h. Flash chromatography (Et_2O/hexane 15:85) afforded **14as** (67.7 mg, 55%, *E*/*Z* = 56/44) as a white solid, and **15as**[48] (19 mg, 15%). *E*-**14as**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40−7.24 (m, 10H), 6.97 (d, J = 1.8 Hz, 1H), 6.06 (br s, 1H), 5.79 (d, J = 3.6 Hz, 1H), 4.69 (d, J = 11.3 Hz, 1H), 4.62 (d, J = 11.3 Hz, 1H), 4.52−4.49 (m, 2H), 4.42 (d, J = 3.6 Hz, 1H), 4.33−4.27 (m, 1H), 3.16 (dd, J = 14.1 Hz, J = 6.6 Hz, 1H), 2.54 (ddd, J = 14.1 Hz, J = 8.6 Hz, J = 1.8 Hz, 1H), 1.53 (s, 3H), 1.52 (s, 3H), 1.31 (s, 3H), 1.28 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.0, 135.4, 132.9, 129.7, 129.1, 128.4, 128.2, 128.0, 127.0, 126.9, 113.4, 109.0, 103.9, 87.2, 81.2, 77.3, 74.1, 72.3, 71.3, 31.5, 26.8, 26.7, 26.4, 24.7. LRMS (FAB^+) *m*/*z* (%) 512 [11, $(M + H)^+$], 454 [15, $(M - C(CH_3)_2 - CH_3)^+$], 393 (38), 322 (64). HRMS (FAB^+) calcd for $C_{28}H_{34}NO_6S$ $(M + H)^+$ 512.2107, found 512.2097. *E*,*Z*-**14as**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43−7.14 (m, $20H_{E,Z}$), 6.97 (d, J = 1.8 Hz, $1H_E$), 6.54 (s, $1H_Z$), 6.06 (br s, $1H_E$), 6.03 (br s, $1H_Z$), 5.79 (d, J = 3.6 Hz, $2H_{E,Z}$), 4.82−4.47 (m, $9H_{E,Z}$), 4.42 (d, J = 3.6 Hz, $1H_E$), 4.34−4.16 (m, $2H_{E,Z}$), 3.16 (dd, J = 14.1 Hz, J = 6.6 Hz, $1H_E$), 2.72 (m, $2H_Z$), 2.54 (ddd, J = 14.1 Hz, J = 8.6 Hz, J = 1.8 Hz, $1H_E$), 1.53 (s, 6H), 1.52 (s, 6H), 1.32 (s, 3H), 1.31 (s, 3H), 1.28 (s, 6H).

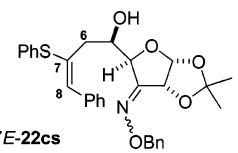
Cyclohexanamine 14at. Prepared by procedure A from **12a** (53 mg, 0.13 mmol), AIBN (22 mg, 0.13 mmol), and Bu_3SnH (71 μL, 0.26 mmol) in dry toluene (6.6 mL). Reaction time: 2 h. Flash

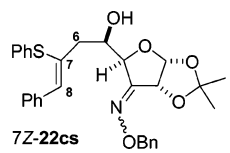
(48) Although the ^{1}H and the ^{13}C NMR spectra of this chromatographic fraction are both very complex, the presence of diagnostic resonances for the carbon atom of the C═N group (δ 157.08 and 157.06 ppm) and for the terminal vinyl proton in $-CH_2-CH{=}CHSPh$ [δ 6.29 ppm (dt, J = 9.3 Hz, J = 1.4 Hz, J = 1.4 Hz, 1H) for the C═C *Z* isomer and δ 6.14 ppm (dt, J = 15.0 Hz, J = 1.2 Hz, J = 1.2 Hz, 1H) for the C═C *E* isomer) strongly suggest it contains a mixture of geometric isomers of the vinyl sulfide **15as** shown below.



(49) Alkenyltins can couple with a wide variety of organic halides and triflates and with acid chlorides. For reviews see: Mitchell, T. N. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds; Wiley-VCH: New York, 2004; Vol. 1, Chapter 3.

(50) When the cyclization of **17c** (**17**, R′ = Ph) to **20cs** was performed using a 450-W medium-pressure mercury lamp (Table 2, entry 12), the reaction was clean enough to allow the isolation of two other products that were tentatively identified (^{1}H NMR, NOE data, and MS) as the noncyclized PhSH adducts 7*E*-**22cs** and 7*Z*-**22cs** (20%). They both appear to be a mixture of geometric isomers around the C═N bond. A NOE observed for H6 in 7*Z*-**22cs**, but not in 7*E*-**22cs**, on irradiation of H8, allowed assignation of the configuration of the C═C bond. See Supporting Information for details.





(51) Protic and Lewis acids have been reported to favour addition of radicals to ketoxime ethers, see for example ref 19.

chromatography (hexane to EtOAc/hexane 5:95) afforded *E*-**14at** (56 mg, 61%) as a white solid: mp = 68−69 °C (Et_2O/hexane). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.34−7.23 (m, 5H), 6.71 (d, J = 1.9 Hz, J_{Sn-H} = 61.2 Hz, 1H), 6.03 (br s, 1H), 5.74 (d, J = 3.5 Hz, 1H), 4.63 (d, J = 11.0 Hz, 1H), 4.58 (d, J = 11.0 Hz, 1H), 4.56−4.53 (m, 2H), 4.34 (d, J = 3.5 Hz, 1H), 4.27−4.20 (m, 1H), 2.72 (ddd, J = 13.7 Hz, J = 9.4 Hz, J = 1.9 Hz, 1H), 2.64 (dd, J = 13.7 Hz, J = 6.6 Hz, 1H), 1.56−1.48 (m, 12 H), 1.36−1.26 (m, 12 H), 1.07−0.94 (m, 6H), 0.88 (t, J = 7.2 Hz, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.7, 137.3, 131.5, 128.3, 128.1, 127.8, 113.3, 108.8, 103.7, 88.1, 81.8, 77.4, 74.2, 73.5, 72.0, 38.9, 29.2, 27.3, 26.9, 26.6, 26.4, 24.5, 13.7, 10.3. LRMS (FAB$^+$) *m*/*z* (%) 694 [78, ($M^{120}Sn$ + H)$^+$], 693 [39, ($M^{119}Sn$ + H)$^+$], 692 [61, ($M^{118}Sn$ + H)$^+$], 636 [87, ($M^{120}Sn$ − Bu)$^+$], 635 [44, ($M^{119}Sn$ − Bu)$^+$], 634 [69, ($M^{118}Sn$ − Bu)$^+$]. Anal. Calcd for $C_{34}H_{55}NO_6Sn$, C 58.97, H 8.01, N 2.02. Found: C 59.08, H 8.26, N 2.09. Z-**14at**: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.38−7.29 (m, 5H), 6.13 (s, J_{Sn-H} = 50.9 Hz, 1H), 5.59 (d, J = 3.3 Hz, 1H), 4.98−4.95 (m, 2H), 4.88 (d, J = 12.1 Hz, 1H), 4.79 (d, J = 5.2 Hz, 1H), 4.27 (m, 1H), 4.19 (m, 1H), 3.48 (dd, J = 15.5 Hz, J = 4.1 Hz, 1H), 2.69 (dd, J = 15.5 Hz, J = 1.1 Hz, 1H), 1.65−1.27 (m, 24 H), 1.08−1.03 (m, 6H), 0.88 (t, J = 7.2 Hz, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.9, 135.4, 134.1, 128.5, 127.8, 126.5, 111.8, 109.5, 102.6, 82.9, 79.1, 78.7, 76.7, 73.9, 72.2, 39.2, 29.2, 27.3, 27.2, 26.6, 26.2, 24.3, 13.8, 10.5. LRMS (ESI-TOF) *m*/*z* (%) 625 [100, ($M^{120}Sn$ − Bn + Na)$^+$], 624 [68, ($M^{119}Sn$ − Bn + Na)$^+$], 623 [91, ($M^{118}Sn$ − Bn + Na)$^+$]. HRMS (ESI-TOF) calcd for $C_{27}H_{48}NNaO_6{}^{120}Sn$ (M − Bn + Na)$^+$ 625.2401, found 625.2219.

Cyclohexenamine 20bs and Cyclopentanamine 21bs. Prepared by procedure B from **17b** (48 mg, 0.12 mmol) and thiophenol [14 μL + 5 μL (added after 4 h), 0.18 mmol] in dry benzene (3 mL). Irradiation time: 6 h. Flash chromatography (EtOAc/hexane 20:80 to 25:75) afforded **20bs** (15 mg, 24%) and **21bs** (12.3 mg, 20%) as oils. **20bs**: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.29−7.21 (m, 10H), 6.29 (s, 1H), 5.89 (d, J = 3.6 Hz, 1H), 5.09 (d, J = 3.6 Hz, 1H), 4.66 (s, 2H), 4.63 (d, J = 3.7 Hz, 1H), 4.38 (m, 1H), 3.46 (s, 3H), 3.09 (dd, J = 18.4 Hz, J = 7.5 Hz, 1H), 2.75 (dd, J = 18.4 Hz, J = 9.8 Hz, 1H), 2.10 (d, J = 10.3 Hz, 1H), 1.55 (s, 3H), 1.32 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.7, 151.5, 136.8, 135.1, 129.7, 129.1, 128.7, 128.4, 128.1, 127.0, 127.5, 113.9, 105.8, 88.1, 83.8, 78.7, 77.4, 72.0, 52.2, 41.0, 27.2, 27.0. LRMS (FAB$^+$) *m*/*z* (%) 500 [33, (M + H)$^+$], 442 [40, (M + H − OC(CH$_3$)$_2$)$^+$]. HRMS (FAB$^+$) calcd for $C_{26}H_{30}NO_7S$ (M + H)$^+$ 500.1743, found 500.1755. IR (CsI) 3486, 3272, 3061−2988−2950, 1720, 1583 cm^{-1}. **21bs** (isolated as an inseparable 55:45 mixture of geometric isomers): ^1H NMR ($CDCl_3$, 300 MHz) δ 7.40−7.21 (m, 20H), 6.53 (br s, 1H), 6.30 (br s, 1H), 5.81 (d, J = 3.4 Hz, 1H), 5.79 (d, J = 3.4 Hz, 1H), 5.18 (d, J = 3.4 Hz, 1H), 5.05 (d, J = 3.4 Hz, 1H), 4.77−4.55 (m, 5H), 4.40 (d, J = 2.0 Hz, 1H), 4.30 (m, 1H), 4.08 (m, 1H), 3.84 (s, 3H), 3.54 (s, 3H), 3.22 (dd, J = 17.7 Hz, J = 7.3 Hz, 1H), 3.42−2.31 (m, 2H), 2.21 (dd, J = 17.2 Hz, J = 10.4 Hz, 1H), 2.12 (d, J = 10.5 Hz, 1H), 1.75 (br s, 1H), 1.54 (s, 6H), 1.35 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.0, 166.3, 142.2, 137.0, 136.9, 133.4, 133.0, 131.7, 130.1, 129.6, 129.2, 129.0, 128.6, 128.4, 128.3, 128.3, 128.2, 127.8, 127.1, 126.3, 113.7, 113.3, 105.6, 104.2, 88.6, 86.1, 82.6, 82.2, 77.9, 77.2, 76.9, 72.4, 71.4, 67.5, 52.3, 52.1, 40.5, 34.1, 27.4, 27.3, 27.2, 26.8. LRMS (FAB$^+$) *m*/*z* (%) 500 [28, (M + H)$^+$]. IR (CsI) 3484, 3276, 3061-2988-2936, 1723, 1582 cm^{-1}.

Cyclohexenamine 20bt$_2$ and Cyclopentanamine 21bt$_2$. Prepared by procedure A from **17b** (53.5 mg, 0.14 mmol), AIBN (24 mg, 0.14 mmol) and Ph_3SnH (70 μL, 0.27 mmol) in dry toluene (6.8 mL). Reaction time: 4.5 h. Flash chromatography (EtOAc/hexane 5:95 to 20:80) afforded **20bt$_2$** (9.5 mg, 9%) as a colorless oil and *E*-**21bt$_2$** (76.4 mg, 75%) as a white foam. **20bt$_2$**: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.61−7.23 (m, 20H), 6.57 (s, 1H), 5.79 (d, J = 3.6 Hz, 1H), 5.09 (d, J = 3.6 Hz, 1H), 4.65 (ABq, J = 11.4 Hz, 2H), 4.55 (d, J = 2.1 Hz, 1H), 4.18 (m, 1H), 3.29 (s, 3H), 2.78 (dd, J = 18.9 Hz, J = 5.3 Hz, 1H), 2.40 (dd, J = 18.9 Hz, J = 10.2 Hz, 1H), 1.70 (d, J = 9.8 Hz, 1H), 1.60 (s, 3H), 1.37 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.0, 163.5, 139.7, 137.0, 136.9, 135.7, 128.8, 128.5, 128.4, 128.2, 127.9, 113.5, 104.4, 83.8, 83.5, 76.9, 72.0, 67.3, 52.0, 38.2, 27.0, 26.9. LRMS (FAB$^+$) *m*/*z* (%) 742 [10, ($M^{120}Sn$ + H)$^+$], 741 [6, ($M^{119}Sn$ + H)$^+$], 740 [9, ($M^{118}Sn$ + H)$^+$], 664 [100, ($M^{120}Sn$ − Ph)$^+$], 663 [50, ($M^{119}Sn$ − Ph)$^+$], 662 [76, ($M^{118}Sn$ − Ph)$^+$]. HRMS (ESI-TOF) calcd for $C_{38}H_{40}NO_7{}^{120}Sn$ (M + H)$^+$ 742.1829, found 742.1826. *E*-**21bt$_2$**: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.68−7.19 (m, 20H), 6.29 (s, 1H), 5.82 (d, J = 3.4 Hz, 1H), 5.28 (d, J = 3.4 Hz, 1H), 4.82 (d, J = 11.3 Hz, 1H), 4.68 (d, J = 3.5 Hz, 1H), 4.61 (d, J = 11.3 Hz, 1H), 4.22 (m, 1H), 3.35 (s, 3H), 2.65 (dd, J = 16.3 Hz, J = 6.9 Hz, 1H), 2.25 (dd, J = 16.3 Hz, J = 10.6 Hz, 1H), 2.05 (br s, 1H), 1.52 (s, 3H), 1.34 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.1, 157.0, 137.1, 137.0, 136.7, 135.3, 129.3, 128.7, 128.4, 128.0, 127.8, 113.7, 105.6, 88.1, 86.4, 78.3, 76.1, 71.9, 51.1, 42.8, 27.4, 27.0. LRMS (FAB$^+$) *m*/*z* (%) 742 [11, (M^{120}Sn + H)$^+$], 741 [7, (M^{119}Sn + H)$^+$], 740 [9, (M^{118}Sn + H)$^+$], 574 [4, (M^{120}Sn − Bn − CO$_2$Me − OH)$^+$], 573 [2, (M^{119}Sn − Bn − CO$_2$Me − OH)$^+$], 572 [3, (M^{118}-Sn − Bn − CO$_2$Me − OH)$^+$]. HRMS (FAB$^+$) calcd for $C_{38}H_{40}$-$NO_7{}^{119}Sn$ (M + H)$^+$ 741.1838, found 741.1848.

Cyclohexenamine 20bt$_1$ and Cyclopentanamine 21bt$_1$. Prepared by procedure A from **17b** (50.3 mg, 0.13 mmol), AIBN (23 mg, 0.14 mmol) and Bu_3SnH (70 μL, 0.26 mmol) in dry toluene (6.4 mL). Reaction time: 1.25 h. Flash chromatography (EtOAc/hexane 5:95 to 10:90) afforded **20bt$_1$** (23.5 mg, 26%) and *E*-**21bt$_1$** (47 mg, 53%) as colorless oils. **20bt$_1$**: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.32−7.22 (m, 5H), 6.45 (br s, 1H), 5.66 (d, J = 3.4 Hz, 1H), 5.06 (d, J = 3.4 Hz, 1H), 4.55 (ABq, J = 11.5 Hz, 2H), 4.49 (d, J = 1.5 Hz, 1H), 4.11 (m, 1H), 3.77 (s, 3H), 2.76 (dd, J = 18.3 Hz, J = 5.4 Hz, 1H), 2.45 (dd, J = 18.3 Hz, J = 10.3 Hz, 1H), 1.76 (br s, 1H), 1.58 (s, 3H), 1.51−1.44 (m, 6H), 1.34 (s, 3H), 1.31−1.25 (m, 6H), 0.98−0.94 (m, 6H), 0.87 (t, J = 7.3 Hz, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.7, 167.5, 137.2, 133.4, 128.4, 128.3, 127.8, 113.3, 104.4, 83.8, 83.6, 76.9, 71.9, 67.4, 52.1, 37.7, 29.1, 27.3, 27.1, 26.8, 13.7, 11.4. LRMS (FAB$^+$) *m*/*z* (%) 682 [6, ($M^{120}Sn$ + H)$^+$], 681 [3, ($M^{119}Sn$ + H)$^+$], 680 [4, ($M^{118}Sn$ + H)$^+$], 624 [100, ($M^{120}Sn$ − Bu)$^+$], 623 [48, ($M^{119}Sn$ − Bu)$^+$], 622 [81, ($M^{118}Sn$ − Bu)$^+$]. HRMS (FAB$^+$) calcd for $C_{28}H_{42}NO_7{}^{120}Sn$ (M − Bu)$^+$ 624.1983, found 624.1988. *E*-**21bt$_1$**: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.34−7.24 (m, 5H), 6.19 (s, 1H), 5.81 (d, J = 3.3 Hz, 1H), 5.16 (d, J = 3.3 Hz, 1H), 4.72 (d, J = 11.4 Hz, 1H), 4.69 (d, J = 3.6 Hz, 1H), 4.56 (d, J = 11.4 Hz, 1H), 4.29 (dddd, J = 10.7 Hz, J = 10.7 Hz, J = 7.1 Hz, J = 3.6 Hz, 1H), 3.71 (s, 3H), 2.64 (dd, J = 15.8 Hz, J = 7.1 Hz, 1H), 2.46 (dd, J = 15.8 Hz, J = 10.7 Hz, 1H), 2.15 (d, J = 10.7 Hz, 1H), 1.55−1.48 (m, 9H), 1.36−1.28 (m, 9H), 1.08−1.01 (m, 6H), 0.88 (t, J = 7.3 Hz, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.6, 152.5, 138.1, 137.4, 128.3, 128.1, 127.8, 113.6, 105.7, 88.1, 86.4, 78.0, 76.1, 72.1, 51.2, 42.2, 28.9, 27.5, 27.2, 27.0, 13.6, 11.0. LRMS (FAB$^+$) *m*/*z* (%) 682 [38, (M^{120}-Sn + H)$^+$], 681 [21, ($M^{119}Sn$ + H)$^+$], 680 [33, ($M^{118}Sn$ + H)$^+$], 624 [42, ($M^{120}Sn$ − Bu)$^+$], 623 [27, ($M^{119}Sn$ − Bu)$^+$], 622 [49, ($M^{118}Sn$ − Bu)$^+$], 534 [100, ($M^{120}Sn$ − OC(CH$_3$)$_2$ − Bu − OH − Me)$^+$], 533 [45, ($M^{119}Sn$ − OC(CH$_3$)$_2$ − Bu − OH − Me)$^+$], 532 [78, ($M^{118}Sn$ − OC(CH$_3$)$_2$ − Bu − OH − Me)$^+$]. HRMS (FAB$^+$) calcd for $C_{32}H_{52}NO_7{}^{119}Sn$ (M + H)$^+$ 681.2687, found 681.2691.

Cyclohexenamine 20bd. A solution of **17b** (40 mg, 0.10 mmol) and benzophenone (19 mg, 0.10 mmol) in 1,3-dioxolane (2.5 mL, 0.04 M) was deoxygenated by bubbling argon for 10 min. The mixture, maintained at <40 °C, was externally irradiated with a 450 W Hanovia medium-pressure mercury lamp until **17b** was consumed (TLC; irradiation time 2.25 h). Solvent removal, followed by flash chromatography (EtOAc/hexane 35:65), afforded **20bd** (31 mg, 65%) as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.34−7.27 (m, 5H), 6.19 (s, 1H), 5.77 (d, J = 3.4 Hz, 1H), 5.42 (s, 1H), 5.25 (d, J = 3.4 Hz, 1H), 4.72 (d, J = 11.1 Hz, 1H), 4.56 (d, J = 11.1 Hz, 1H), 4.41 (d, J = 1.9 Hz, 1H), 4.13−4.09 (m, 1H), 4.05−3.89 (m, 4H), 3.81 (s, 3H), 2.54 (dd, J = 17.4 Hz, J = 5.7 Hz, 1H), 2.26 (dd, J = 17.4 Hz, J = 10.5 Hz, 1H), 1.90 (d, J = 9.8

Hz, 1H), 1.55 (s, 3H), 1.34 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.6, 141.6, 137.1, 128.9, 128.5, 128.2, 127.7, 113.2, 104.2, 101.6, 82.5, 82.2, 76.8, 71.9, 67.1, 65.7, 52.1, 27.2, 26.8, 26.7. LRMS (FAB^+) *m*/*z* (%) 464 [8, $(M + H)^+$], 391 [22, (M + H − dioxolanyl)$^+$]. HRMS (FAB^+) calcd for $C_{23}H_{30}NO_9$ $(M + H)^+$ 464.1920, found 464.1924.

Cyclohexenamine 20cs. Prepared by procedure B from **17c** (76.6 mg, 0.18 mmol) and thiophenol (20.5 μL, 0.19 mmol, one portion) in dry benzene (9.4 mL). Irradiation time: 3 h. Flash chromatography (EtOAc/hexane 10:90 to 20:80) afforded **20cs** (73 mg, 75%) as a white solid, and 7*E*-**22cs**[50] (6.1 mg, 6%) and 7*Z*-**22cs**[50] (6.3 mg, 6%) as oils. **20cs**: mp = 168−170 °C (CH_2Cl_2/hexane). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.43−7.16 (m, 15H), 6.06 (s, 1H), 5.85 (d, J = 3.3 Hz, 1H), 4.95 (d, J = 11.1 Hz, 1H), 4.81 (d, J = 11.1 Hz, 1H), 4.62 (d, J = 2.2 Hz, 1H), 4.34 (d, J = 3.3 Hz, 1H), 4.4−4.3 (m, 1H), 2.51 (dd, J = 16.8 Hz, J = 6.3 Hz, 1H), 2.35 (dd, J = 16.8 Hz, J = 10.1 Hz, 1H), 1.81 (d, J = 10.2 Hz, 1H), 1.55 (s, 3H), 1.24 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.5, 136.7, 134.9, 134.5, 133.5, 131.8, 130.3, 128.9, 128.5, 128.3, 128.0, 127.7, 127.1, 113.6, 104.0, 83.2, 82.9, 76.2, 72.3, 67.4, 34.4, 27.2, 26.8. LRMS (FAB^+) *m*/*z* (%) 518 [28, $(M + H)^+$], 395 [100, (M − NHOBn)$^+$].

Cyclohexenamine 20ct$_1$. Prepared by procedure A from **17c** (60.7 mg, 0.15 mmol), AIBN (26 mg, 0.15 mmol), and Bu_3SnH (80 μL, 0.29 mmol) in dry toluene (7.4 mL). Reaction time: 1.75 h. Flash chromatography (EtOAc/hexane 10:90 to 20:80) afforded **20ct$_1$** (94.7 mg, 91%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35−7.23 (m, 10H), 5.98 (s, 1H), 5.76 (d, J = 3.3 Hz, 1H), 4.89 (d, J = 11.3 Hz, 1H), 4.75 (d, J = 11.3 Hz, 1H), 4.59 (d, J = 2.3 Hz, 1H), 4.34 (dddd, J = 10.1 Hz, J = 10.1 Hz, J = 5.9 Hz, J = 2.3 Hz, 1H), 4.24 (d, J = 3.3 Hz, 1H), 2.73 (dd, J = 17.0 Hz, J = 5.9 Hz, 1H), 2.37 (dd, J = 17.0 Hz, J = 10.1 Hz, 1H), 1.83 (J = 10.1 Hz, 1H), 1.51 (s, 3H), 1.40−1.14 (m, 15 H), 0.83 (t, J = 7.1 Hz, 9H), 0.55−0.46 (m, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 147.2, 142.1, 141.8, 137.2, 130.8, 128.4, 128.2, 128.1, 127.9, 127.4, 113.4, 104.1, 83.9, 83.1, 75.9, 72.1, 67.7, 37.0, 29.0, 27.2, 27.1, 26.7, 13.6, 10.1. LRMS (FAB^+) *m*/*z* (%) 700 [9, $(M^{120}Sn + H)^+$], 699 [5, $(M^{119}Sn + H)^+$], 698 [7, $(M^{118}Sn + H)^+$], 642 [100, $(M^{120}Sn - Bu)^+$], 641 [48, $(M^{119}Sn - Bu)^+$], 640 [75, $(M^{118}Sn - Bu)^+$]. HRMS (FAB^+) calcd for $C_{36}H_{54}NO_5{}^{119}Sn$ $(M + H)^+$ 699.2946, found 699.2951.

Acknowledgment. This work was supported by the Spanish Ministries of Science and Technology (Project BQU2002-01176) and Education and Science (Project CTQ2005-02338) in collaboration with ERDF, the Xunta de Galicia (through Project PGIDIT05BTF20901PR and a fellowship to M.F.) and the University of Santiago de Compostela (through a postdoctoral contract to M.F.).

Supporting Information Available: Experimental procedures and characterization data for **12a** and **17a−c** and their synthetic precursors. NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO060883Y